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Efficacy of the Non-D2 Mechanism of Ulotaront on Positive, Negative, and Cognitive Symptoms of Schizophrenia: A Systematic Review and Meta-Analysis

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Abstract

Background: Schizophrenia is a chronic psychiatric disorder characterized by positive symptoms, negative symptoms, cognitive impairment, and substantial functional disability. Conventional antipsychotic medications primarily act through dopamine D2-receptor antagonism or partial agonism. Although these treatments are effective against positive symptoms in many patients, negative symptoms and cognitive dysfunction frequently persist. Ulotaront (SEP-363856), an investigational psychotropic agent with trace amine-associated receptor 1 (TAAR1) and serotonin 5-HT1A receptor agonist activity, represents a pharmacological approach that does not depend on direct D2-receptor binding.

Objective: To systematically evaluate the efficacy and safety of ulotaront in schizophrenia, with particular emphasis on positive symptoms, negative symptoms, and cognitive impairment, and to critically synthesize available randomized evidence.

Methods: A structured evidence synthesis was developed using published randomized controlled trials, clinical trial reports, existing systematic reviews, and relevant longitudinal studies. The methodological

framework follows PRISMA 2020 and Cochrane recommendations. Randomized placebo-controlled evidence was prioritized for comparative efficacy, while open-label extension studies were considered supportive evidence. Published meta-analytic estimates were examined without duplicating participants across trial reports.

Results: Three randomized trials involving participants were identified in a published ulotaront dose-response meta-analysis. The initial phase II trial involving 245 participants demonstrated a significantly greater reduction in Positive and Negative Syndrome Scale (PANSS) total scores with ulotaront than placebo at four weeks (between-group difference −7.5 points; 95% confidence interval [CI], −11.9 to −3.0). However, the subsequent phase III DIAMOND 1 and DIAMOND 2 trials did not achieve their primary efficacy endpoints. A published dose-response meta-analysis reported a standardized mean difference of −0.23 (95% CI, −0.43 to −0.02) for PANSS total score at 100 mg, with a negative-symptom estimate of −0.28 (95% CI, −0.48 to −0.08). Evidence supporting cognitive improvement remained insufficient for a definitive conclusion. Short-term tolerability findings suggested limited extrapyramidal and metabolic effects, although adverse events and long-term safety require further evaluation.

Conclusion: Ulotaront offers a biologically distinct non-D2 therapeutic strategy for schizophrenia. Although early clinical findings were encouraging, the failure of two large phase III trials to demonstrate statistically significant superiority over placebo introduces substantial uncertainty regarding its overall antipsychotic efficacy. Potential effects on negative symptoms and cognition require confirmation in adequately powered trials using dedicated outcome measures.

Keywords: Ulotaront, SEP-363856, Schizophrenia, TAAR1, 5-HT1A, Non-D2 Antipsychotic, Positive Symptoms, Negative Symptoms, Cognitive Impairment, Systematic Review, Meta-Analysis.

Introduction

Schizophrenia is a chronic and disabling psychiatric disorder characterized by a heterogeneous combination of positive symptoms, negative symptoms, cognitive impairment, affective disturbances, and functional deterioration. Positive symptoms, including hallucinations, delusions, and disorganized thought, are generally the most recognizable manifestations of the illness, whereas negative symptoms and cognitive dysfunction frequently contribute substantially to long-term disability and impaired social and occupational functioning.[1]

The pharmacological treatment of schizophrenia has historically been dominated by antipsychotic agents that modulate dopamine D2-receptor signaling. Antipsychotics are effective in reducing acute psychotic symptoms in many patients; however, their effectiveness against persistent negative symptoms and cognitive impairment remains limited. In addition, dopamine D2-receptor blockade can contribute to extrapyramidal symptoms, hyperprolactinemia, and other treatment-related adverse effects, creating a continuing need for pharmacologically distinct therapeutic approaches[2]. Negative symptoms represent an especially important unmet therapeutic need in schizophrenia. They include diminished emotional expression, avolition, anhedonia, asociality, and alogia and can persist despite adequate control of positive symptoms. Persistent negative symptoms are associated with poorer functional

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outcomes and reduced quality of life. Their complex neurobiology, involving interactions among dopaminergic, glutamatergic, serotonergic, and other neurotransmitter systems, has encouraged investigation of treatment strategies that extend beyond conventional D2-receptor antagonism[3].

Cognitive impairment is another core component of schizophrenia and may involve attention, processing speed, working memory, verbal and visual learning, executive function, and social cognition. Cognitive deficits can occur independently of the severity of positive symptoms and are strongly associated with functional disability. Despite extensive clinical research, currently available antipsychotic treatments have not consistently demonstrated clinically meaningful improvements across the broad range of cognitive domains affected in schizophrenia[4].

These limitations have stimulated interest in novel pharmacological targets that can influence psychosis without directly blocking dopamine D2 receptors. One such target is the trace amine-associated receptor 1 (TAAR1), a G-protein-coupled receptor expressed within neural circuits involved in monoaminergic neurotransmission. Experimental evidence suggests that TAAR1 activation can regulate dopaminergic and serotonergic signaling and may influence neuronal circuits implicated in psychosis, cognition, and emotional processing[5]. Ulotaront (SEP-363856) is an investigational psychotropic agent developed as a non-D2-receptor-binding treatment for schizophrenia. Unlike conventional antipsychotic drugs, ulotaront does not exert its primary pharmacological action through direct D2-receptor antagonism. It has agonist activity at TAAR1 and serotonin 5-HT1A receptors, providing a mechanistically distinct approach to modulation of neurotransmitter systems relevant to schizophrenia[6]. The therapeutic rationale for TAAR1 agonism derives partly from preclinical studies demonstrating effects on dopaminergic and serotonergic neurotransmission without direct postsynaptic D2-receptor blockade. Activation of TAAR1 may regulate excessive dopaminergic activity associated with psychosis while potentially influencing cortical and limbic circuits involved in motivation and cognition[7]. However, the precise contribution of TAAR1 versus 5-HT1A receptor activity to the clinical effects of ulotaront remains incompletely established. The first major randomized clinical trial of ulotaront provided encouraging evidence for this non-D2 approach. In a four-week, randomized, double-blind, placebo-controlled phase II study involving patients with an acute exacerbation of schizophrenia, ulotaront produced a significantly greater improvement in total Positive and Negative Syndrome Scale (PANSS) score compared with placebo. The study therefore provided initial clinical evidence that meaningful antipsychotic effects could potentially be achieved without direct D2-receptor blockade[8].

Importantly, exploratory analyses of the phase II trial also identified improvements in negative symptoms. Changes in PANSS negative symptoms and the Brief Negative Symptom Scale (BNSS) suggested that ulotaront might have effects extending beyond the conventional treatment of hallucinations and delusions8. These observations were particularly relevant because persistent negative symptoms remain one of the major limitations of contemporary schizophrenia pharmacotherapy.

Longer-term open-label investigations subsequently examined the continued efficacy and safety of ulotaront. Improvements in overall psychopathology, negative

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symptoms, functioning, and selected cognitive measures were observed during extended treatment. However, interpretation of these findings is limited by the absence of a concurrent placebo control and the possibility of regression to the mean, practice effects, natural fluctuations in illness severity, and other biases inherent to open-label studies[9]. The subsequent development program provided a more complex picture. The phase III DIAMOND 1 and DIAMOND 2 trials were designed to provide confirmatory evidence regarding the efficacy of ulotaront in acute schizophrenia. Neither study demonstrated statistically significant superiority of ulotaront over placebo on its prespecified primary PANSS total-score endpoint[10]. These findings are important because they introduce uncertainty regarding the reproducibility of the positive results observed in the earlier phase II study.

The discrepancy between early and later clinical findings illustrates the importance of evaluating the totality of available evidence rather than interpreting an individual clinical trial in isolation. Differences in patient populations, placebo response, study design, treatment duration, baseline illness characteristics, and trial execution may contribute to variation in observed treatment effects. Consequently, quantitative synthesis of available randomized evidence can provide a more comprehensive assessment of the consistency and magnitude of treatment effects[11]. Recent systematic and meta-analytic investigations have specifically examined the dose-response relationship of ulotaront in schizophrenia. One published dose-response meta-analysis incorporating three randomized trials and 1,144 participants reported a small estimated improvement in PANSS total score at a 100-mg dose. The same analysis suggested an improvement in negative symptoms, although the magnitude of benefit was modest and the results must be interpreted in the context of the unsuccessful confirmatory phase III trials[12]. Evidence regarding cognitive outcomes remains comparatively limited. Because cognition represents an important determinant of functional recovery, potential effects of TAAR1/5-HT1A agonism on attention, processing speed, working memory, and learning are of particular interest. Nevertheless, differences in cognitive instruments, exploratory outcome definitions, and limited availability of adequately powered randomized cognitive endpoints currently prevent definitive conclusions regarding a specific cognitive benefit of ulotaront[13].

Safety and tolerability also represent important considerations when evaluating a novel non-D2 antipsychotic. Early studies suggested relatively limited effects on extrapyramidal symptoms, prolactin concentrations, and metabolic parameters compared with the adverse-effect profile commonly associated with dopamine-receptor blockade. However, individual adverse events have been reported, and the relatively limited duration and size of controlled trials mean that long-term safety cannot yet be fully characterized[14].

Given the continuing need for treatments addressing positive symptoms while potentially improving negative and cognitive domains without direct D2-receptor antagonism, ulotaront represents an important subject for systematic evaluation. The coexistence of encouraging phase II findings, exploratory evidence concerning negative and cognitive symptoms, and negative primary outcomes from subsequent phase III trials creates a clinically relevant evidence gap. Therefore, the present systematic review and meta-analysis aims to critically evaluate the efficacy of ulotaront on positive symptoms,

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negative symptoms, and cognitive impairment in schizophrenia, while also examining overall psychopathology and treatment tolerability. By synthesizing the available randomized evidence and distinguishing established findings from exploratory observations, this review seeks to clarify the current evidence for the non-D2 mechanism of ulotaront and identify priorities for future clinical investigation[15].

Materials and Methods

Study Design

This systematic review and meta-analysis was designed to evaluate the efficacy and tolerability of ulotaront (SEP-363856), a non-D2-receptor-binding investigational antipsychotic, in patients with schizophrenia. The review specifically focused on its effects on positive symptoms, negative symptoms, and cognitive impairment, with overall psychopathology and treatment-emergent adverse events considered as additional outcomes.

The methodology was structured in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 recommendations. The review question and eligibility criteria were established before data extraction. Where possible, the methodological approach was aligned with recommendations of the Cochrane Collaboration for systematic reviews of interventions.

Review Question

The review addressed the following question:

Among patients with schizophrenia, does treatment with ulotaront, compared with placebo or another appropriate comparator, improve positive symptoms, negative symptoms, and cognitive function while maintaining an acceptable safety profile ?. The question was structured according to the PICOS framework.

Table 1. PICOS framework

Component	Definition
Population (P)	Adults or adolescents diagnosed with schizophrenia according to recognized diagnostic criteria
Intervention (I)	Ulotaront (SEP-363856), administered at any clinically investigated dose
Comparator (C)	Placebo or an appropriate active comparator
Outcomes (O)	Positive symptoms, negative symptoms, cognitive function, total psychopathology, global clinical status, treatment response, discontinuation, and adverse events
Study design (S)	Randomized controlled trials; longitudinal/open-label studies considered for supplementary safety and longer-term evidence

Reporting Guidelines

The review was planned and reported according to the **PRISMA 2020 statement**. The PRISMA framework was used to organize identification, screening, eligibility assessment, inclusion, and reporting of relevant studies.

Information Sources

A comprehensive literature search was designed to identify published and unpublished evidence concerning ulotaront in schizophrenia. The following electronic databases and trial registries were considered:

1. PubMed/Medline
2. Embase
3. Scopus
4. Web of Science
5. Cochrane Central Register of Controlled Trials (CENTRAL)

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6. ClinicalTrials.gov
7. WHO International Clinical Trials Registry Platform (ICTRP)

Search Strategy

The search strategy combined terms relating to the intervention and disease.

The principal PubMed search strategy was:

("ulotaront" OR "SEP-363856") AND ("schizophrenia" OR "schizophrenic disorder" OR "psychosis" OR "psychotic disorder")

Additional searches incorporated outcome-related terms:

("ulotaront" OR "SEP-363856") AND ("schizophrenia" OR "psychosis") AND ("positive symptoms" OR "negative symptoms" OR cognition OR cognitive OR PANSS OR BNSS)

Database-specific controlled vocabulary, including MeSH and Emtree terms, would be adapted where appropriate.

The search was designed to identify studies published from database inception through **September 2026**.

Eligibility Criteria

Inclusion criteria

Studies were eligible when they fulfilled the following criteria:

- Participants had a diagnosis of schizophrenia.
- Ulotaront was administered as the investigational intervention.
- The study included placebo or another appropriate comparator for comparative efficacy analyses.
- At least one relevant clinical outcome was reported.
- Randomized controlled trials were eligible for the principal meta-analysis.
- Published extension studies were considered for supplementary assessment of longer-term efficacy and safety.
- Studies provided sufficient information to determine the direction or magnitude of treatment effect.

Exclusion criteria

The following were excluded:

- Animal and preclinical studies.
- In-vitro or laboratory studies without human clinical outcomes.
- Case reports and case series.
- Narrative reviews and editorials.
- Conference material without sufficient numerical outcome data for the intended analysis.
- Studies evaluating ulotaront for conditions other than schizophrenia.
- Duplicate publications reporting the same trial population, unless they provided unique prespecified outcomes.
- Studies without relevant efficacy or safety information.

Study Selection

All retrieved records were screened initially by title and abstract. Potentially relevant articles were subsequently assessed through full-text evaluation.

Duplicate records were removed before eligibility assessment. When multiple publications originated from the same clinical trial, they were linked to the parent trial to prevent double-counting of participants**.**

For quantitative synthesis, the principal publication or the report containing the most complete relevant outcome data was preferentially selected.

The study-selection process was planned to be presented using a PRISMA flow diagram, showing:

1. Records identified.
2. Duplicate records removed.
3. Records screened.
4. Full-text articles assessed.

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5. Articles excluded with reasons.
6. Studies included in qualitative synthesis.
7. Studies included in quantitative synthesis/meta-analysis.

Data Extraction

A standardized data-extraction framework was used to collect information from eligible studies.

The following variables were extracted:

- First author and publication year.
- Clinical trial name.
- Country or study setting.
- Study design.
- Diagnostic criteria.
- Sample size.
- Participant age and sex.
- Duration of illness.
- Baseline symptom severity.
- Ulotaront dose.
- Comparator treatment.
- Treatment duration.
- PANSS total score.
- PANSS positive subscale.
- PANSS negative subscale.
- BNSS score, where available.
- Cognitive outcomes.
- Clinical Global Impression measures.
- Functional outcomes.
- Treatment response.
- Treatment discontinuation.
- Treatment-emergent adverse events.
- Serious adverse events.
- Extrapyramidal symptoms.
- Metabolic outcomes.
- Prolactin-related outcomes.
- Measures of variance, including standard deviation or standard error.
- Number of participants analyzed.
- Follow-up duration.

When several follow-up points were reported, the prespecified acute-treatment endpoint was preferentially used for the principal efficacy analysis.

Primary Outcomes

The primary efficacy outcomes were:

1. Positive symptoms, assessed primarily using the PANSS positive subscale.
2. Negative symptoms, assessed using the PANSS negative subscale and/or BNSS.
3. Cognitive function, assessed using validated neuropsychological instruments.

The principal comparison was the change from baseline to the end of the randomized treatment period.

Secondary Outcomes

Secondary outcomes included:

- PANSS total score.
- Clinical Global Impression-Severity (CGI-S).
- Clinical Global Impression-Improvement (CGI-I).
- Treatment response.
- Functional performance.
- Treatment discontinuation.
- All-cause discontinuation.
- Treatment-emergent adverse events.
- Serious adverse events.
- Extrapyramidal symptoms.
- Changes in metabolic parameters.
- Changes in prolactin concentrations.

Assessment of Risk of Bias

Risk of bias in randomized controlled trials was assessed according to the Cochrane Risk of Bias 2 (RoB 2) framework.

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The following domains were considered:

1. Bias arising from the randomization process.
2. Bias due to deviations from intended interventions.
3. Bias due to missing outcome data.
4. Bias in measurement of the outcome.
5. Bias in selection of the reported result.

Each domain was categorized as having low risk of bias, some concerns, or high risk of bias, according to the RoB 2 framework.

Open-label extension studies were assessed separately because their non-randomized design introduces additional risks of selection, performance, and attrition bias.

Effect Measures

For continuous outcomes measured using the same instrument, the mean difference (MD) with 95% confidence interval (CI) was used.

When studies evaluated the same clinical construct using different validated instruments, the standardized mean difference (SMD) with 95% CI was planned.

For dichotomous outcomes, including treatment response, discontinuation, and adverse events, risk ratios (RRs) with 95% CIs were planned.

For interpretation, a negative MD or SMD for symptom scores indicated a greater reduction in symptoms with ulotaront when the scale was oriented such that lower scores represented improvement.

Meta-analysis

Where at least two clinically comparable studies reported the same outcome, quantitative synthesis was planned using a random-effects model**,** given the expected differences in participant characteristics, treatment doses, treatment duration, and clinical settings.

For PANSS and other continuous outcomes, treatment effects were expressed as MD or SMD with 95% CI according to the measurement scale.

The analysis was designed to avoid combining fundamentally different outcomes merely because they belonged to the same broad symptom domain.

Assessment of Heterogeneity

Statistical heterogeneity was assessed using Cochran's Q test and the I^2 statistic**.**

The approximate interpretation of I^2 was:

- 0–25%: low heterogeneity
- 26–50%: moderate heterogeneity
- 51–75%: substantial heterogeneity
- >75%: considerable heterogeneity

However, I^2 was not interpreted in isolation because its magnitude can be influenced by the number of studies, sample size, and precision of individual estimates.

Clinical heterogeneity was also considered by examining:

- Ulotaront dose.
- Treatment duration.
- Baseline symptom severity.
- Trial phase.
- Patient characteristics.
- Outcome measurement instruments.

Subgroup and Sensitivity Analyses

Where sufficient studies were available, subgroup analyses were planned according to:

- Ulotaront dose.
- Treatment duration.
- Phase II versus phase III trials.
- PANSS versus BNSS assessment of negative symptoms.
- Acute versus longer-term treatment.
- Risk-of-bias category.

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Sensitivity analyses were planned by excluding studies with high risk of bias and by examining the influence of individual trials on the pooled estimate.

Because the number of available randomized ulotaront trials is limited, subgroup analyses were interpreted cautiously and were not considered confirmatory unless supported by adequate numbers of independent studies.

Assessment of Publication Bias

When at least 10 independent studies were available for a specific outcome, publication bias and small-study effects were planned to be assessed using funnel-plot inspection and appropriate statistical tests such as **Egger's regression test**.

Because the ulotaront evidence base is relatively small, formal publication-bias testing may have inadequate statistical power and therefore would not be interpreted as definitive when fewer than 10 studies were available.

Cognitive Outcome Analysis

Cognitive outcomes were analyzed separately from general psychopathology.

Where the same cognitive instrument was used across studies, mean differences were planned. Where different validated cognitive instruments assessed comparable domains, standardized mean differences were planned.

Particular attention was given to:

- Processing speed.
- Attention.
- Working memory.
- Verbal learning.
- Visual learning.
- Executive function.
- Social cognition.

Open-label improvements in cognitive performance were not treated as equivalent to placebo-controlled evidence because practice effects and nonspecific clinical improvement may influence repeated cognitive testing.

Safety Analysis

Safety was evaluated by comparing the frequency of treatment-emergent adverse events between ulotaront and comparator groups.

Particular attention was given to:

- Extrapyramidal symptoms.
- Akathisia.
- Somnolence.
- Gastrointestinal adverse events.
- Anxiety.
- Weight change.
- Metabolic parameters.
- Prolactin abnormalities.
- Serious adverse events.
- Suicidality-related events.
- Treatment discontinuation because of adverse events.

Safety findings were interpreted separately from efficacy outcomes because the relatively short duration of randomized trials limits conclusions regarding long-term safety.

Certainty of Evidence

The overall certainty of evidence for major outcomes was planned to be evaluated using the GRADE framework**,** considering:

- Risk of bias.
- Inconsistency.
- Indirectness.
- Imprecision.
- Publication bias.

Evidence would be classified as high, moderate, low, or very low certainty according to the GRADE approach.

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Management of Duplicate Data

Particular care was taken to avoid duplicate counting because several publications may originate from the same ulotaront clinical development program.

The phase II primary publication, long-term extension publications, and later analyses were treated as reports from related clinical cohorts where appropriate. Participants from a clinical trial were counted only once in a particular quantitative comparison.

Ethical Considerations

Because the study synthesizes data already reported in published clinical trials and does not involve recruitment or direct intervention involving human participants, no new participant-level intervention was undertaken. Ethical approval and informed consent were therefore not required for the systematic review itself. The review nevertheless recognizes that the underlying clinical trials would have required appropriate ethical and regulatory approval.

Discussion

Principal Findings

Ulotaront (SEP-363856) is an investigational antipsychotic developed as a non-D2-receptor-based treatment for schizophrenia. Unlike conventional antipsychotics, ulotaront does not directly antagonize dopamine D2 receptors and instead primarily acts as a trace amine-associated receptor 1 (TAAR1) agonist, with additional activity at the serotonin 5-HT1A receptor [1]. The initial phase II randomized controlled trial demonstrated a significant reduction in PANSS total score compared with placebo, providing preliminary clinical evidence for this novel pharmacological approach[2]. Subsequent phase III studies, however, produced less consistent results, creating uncertainty regarding the reproducibility of the initial efficacy signal[3].

The dose-response meta-analysis of available randomized trials suggested a small reduction in overall schizophrenia symptoms with ulotaront, particularly at higher doses[4]. These findings provide quantitative support for a potential therapeutic effect but must be interpreted alongside the negative findings from confirmatory phase III trials.

Pharmacological Basis

Conventional antipsychotic medications exert their principal therapeutic effects through dopamine D2-receptor blockade or partial agonism[5]. Although this mechanism is effective for acute psychotic symptoms, D2-receptor modulation can contribute to extrapyramidal symptoms, hyperprolactinemia, and other adverse effects.[6]

TAAR1 is a G-protein-coupled receptor involved in the regulation of monoaminergic neurotransmission. Activation of TAAR1 can influence dopaminergic signaling without directly blocking D2 receptors[7]. Preclinical studies have further demonstrated that TAAR1 activation can normalize abnormalities in dopamine and glutamate neurotransmission in experimental models relevant to schizophrenia[8].

These mechanisms provide a biological rationale for investigating TAAR1 agonists as alternative treatments for schizophrenia. Nevertheless, findings from experimental models cannot be assumed to predict clinical efficacy in humans.

Phase II Clinical Evidence

The first major clinical evaluation of ulotaront demonstrated a statistically significant improvement in PANSS total score compared with placebo[5]. This study was important because it provided early evidence that an

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antipsychotic effect might be achieved without direct D2-receptor antagonism.

The observed improvement included several symptom domains and supported further clinical development. However, the relatively short treatment period and limited sample size restricted the ability to establish long-term efficacy.

Phase III Evidence

The subsequent DIAMOND clinical development program was designed to confirm the efficacy observed during phase II testing[3]. The trials enrolled larger populations and evaluated different doses of ulotaront in patients with acute schizophrenia.

Neither DIAMOND 1 nor DIAMOND 2 demonstrated statistically significant superiority over placebo on the prespecified primary PANSS total-score endpoint[3]. These results are important because they indicate that the initial efficacy signal was not consistently reproduced in confirmatory studies.

Placebo Response

A relatively substantial placebo response was observed in the phase III studies[3]. High placebo response is a recognized challenge in schizophrenia trials and may reduce the ability to demonstrate separation between an investigational treatment and placebo[9].

Potential contributors include regression toward the mean, expectancy effects, frequent contact with clinical staff, and differences in symptom assessment [10]. Future studies should therefore use rigorous rater training, centralized assessments where feasible, and standardized recruitment and outcome-assessment procedures.

Positive Symptoms

Positive symptoms such as hallucinations and delusions remain a major target of antipsychotic treatment[5]. The initial clinical trial suggested that ulotaront could improve positive symptoms[2].

However, the pooled evidence from the dose-response analysis produced an uncertain estimate for positive symptoms[4]. The confidence interval included the possibility of no statistically significant treatment effect. Therefore, current evidence does not establish a consistent benefit of ulotaront for positive symptoms across all randomized trials.

Negative Symptoms

Negative symptoms represent an important unmet therapeutic need in schizophrenia and include avolition, anhedonia, asociality, alogia, and diminished emotional expression[11]. They are frequently associated with poor social and occupational functioning.

The available ulotaront studies have generated interest in its potential effects on negative symptoms. The dose-response analysis demonstrated a small estimated improvement in negative symptoms[4]. However, negative symptoms can also be secondary to depression, psychosis, medication effects, or environmental factors[12].

Consequently, improvement in negative symptoms during an acute schizophrenia study should not automatically be interpreted as evidence of efficacy against primary persistent negative symptoms.

Cognitive Symptoms

Cognitive impairment is common in schizophrenia and involves domains such as attention, processing speed, working memory, learning, and executive functioning[13]. These impairments contribute substantially to disability and are not adequately represented by the PANSS.

Exploratory assessments conducted during the ulotaront development program examined cognitive and functional outcomes[14]. Although these findings provide

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preliminary evidence of possible cognitive effects, the available studies were not specifically designed or sufficiently powered to establish a definitive cognitive benefit.

Cognitive and Functional Outcomes

Cognitive improvement is clinically meaningful when it translates into better every day functioning. Schizophrenia-related cognitive impairment can interfere with employment, interpersonal relationships, independent living, and social participation[13].

Exploratory ulotaront studies have included measures of cognition and functional capacity[14]. However, the available evidence remains insufficient to establish whether changes in cognitive performance produce meaningful improvements in real-world functioning.

Long-Term Evidence

A six-month open-label extension study provided additional information regarding continued ulotaront exposure[15]. Participants demonstrated continued reductions in PANSS total scores and other clinical measures during the extension period.

The study also provided preliminary information regarding longer-term tolerability. However, because the extension was open-label and lacked a concurrent control group, the observed improvements cannot be interpreted as definitive evidence of sustained drug efficacy.

Safety Profile

One potential advantage of a non-D2 mechanism is the possibility of reducing adverse effects associated with dopamine receptor blockade. The initial randomized trial reported no major differences between ulotaront and placebo in several measures of extrapyramidal symptoms, prolactin, and metabolic parameters[2].

The open-label extension also reported relatively limited changes in weight and metabolic parameters[15]. These observations are consistent with the pharmacological profile of ulotaront but require confirmation in larger and longer controlled studies.

Metabolic Effects

Metabolic adverse effects are an important concern during long-term antipsychotic treatment. Weight gain, dyslipidemia, and glucose abnormalities can contribute to increased cardiovascular risk[16].

The relatively limited metabolic changes observed during ulotaront treatment are therefore clinically relevant. However, the current evidence is insufficient to establish that ulotaront has a superior metabolic safety profile compared with individual established antipsychotics.

Comparison with Existing Antipsychotics

A network meta-analysis of oral antipsychotic drugs has demonstrated differences among established treatments in both efficacy and tolerability[17]. These findings emphasize that antipsychotic treatment involves balancing symptom control with adverse-effect burden.

Ulotaront differs from these conventional agents because its primary pharmacological mechanism does not involve direct D2-receptor antagonism. Direct head-to-head trials will therefore be necessary to determine how its efficacy and tolerability compare with established antipsychotic therapies.

Heterogeneity of Schizophrenia

Schizophrenia is a clinically and biologically heterogeneous disorder, with substantial variation in symptom profiles, cognitive impairment, illness duration, and treatment response[18]. Such heterogeneity may contribute to variability in response to novel pharmacological treatments.

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Future studies should investigate whether particular clinical or biological characteristics are associated with greater response to TAAR1-based treatment.

Diagnostic and Clinical Heterogeneity

The modern definition of schizophrenia encompasses a heterogeneous collection of symptoms and clinical presentations[19]. This heterogeneity is relevant when interpreting clinical trials because participants may differ substantially in the relative severity of positive, negative, affective, and cognitive symptoms.

Future ulotaront trials should therefore consider symptom-domain-specific outcomes rather than relying exclusively on total PANSS scores.

Acute Efficacy

Evidence from broader antipsychotic meta-analyses indicates that established antipsychotics generally produce meaningful reductions in acute psychotic symptoms[20]. The clinical evidence for ulotaront remains less established because the confirmatory phase III studies did not demonstrate statistically significant superiority over placebo[3].

This distinction is important when interpreting the role of ulotaront within the current schizophrenia treatment landscape.

Persistent Negative Symptoms

Negative symptoms remain difficult to treat pharmacologically. A large meta-analysis of randomized placebo-controlled trials found that treatment effects for negative symptoms vary considerably across interventions.[21]

The signal observed with ulotaront therefore warrants further investigation, particularly in patients with persistent negative symptoms. Dedicated trials should distinguish primary negative symptoms from secondary symptoms related to depression, psychosis, or medication adverse effects.

Cognitive Effects of Antipsychotic Treatment

Cognitive outcomes may differ between antipsychotic treatments, although evidence regarding clinically meaningful cognitive improvement remains variable[22]. Because cognitive impairment contributes strongly to functional disability, future ulotaront research should give cognition a greater role as a prespecified outcome.

Standardized neuropsychological assessments should be combined with functional measures to determine whether cognitive changes translate into practical benefits.

Mechanistic Considerations

The absence of direct D2 antagonism is a defining characteristic of ulotaront and distinguishes it mechanistically from many established antipsychotics[23]. TAAR1-mediated modulation of monoaminergic signaling represents a fundamentally different therapeutic strategy.

However, the presence of a novel mechanism does not itself establish clinical superiority. The ultimate value of this mechanism must be determined through adequately powered clinical trials evaluating efficacy, tolerability, cognition, and functional outcomes.

Broader TAAR1 Evidence

Evidence from the broader TAAR1 literature provides additional support for continued investigation of this receptor system in psychosis[24]. Preclinical and early clinical findings suggest that TAAR1 modulation may influence pathways relevant to schizophrenia.

Nevertheless, the limited number of completed clinical trials means that the therapeutic role of TAAR1 agonism remains incompletely established. Ulotaront therefore

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represents an important clinical test of the broader TAAR1 hypothesis.

Need for long-term controlled evidence

The available six-month extension data are useful for characterizing tolerability but cannot replace long-term randomized evidence[13]. Long-term controlled studies should examine relapse prevention, persistence of negative and cognitive effects, treatment adherence, quality of life, functioning, weight trajectory, metabolic parameters, prolactin, movement disorders, and cardiovascular outcomes. Such studies are especially important because schizophrenia generally requires prolonged treatment. A treatment that has a favorable short-term safety profile but lacks demonstrated long-term efficacy would have limited clinical utility.

Strengths of the current evidence base

Several features strengthen the evidence concerning ulotaront. The initial efficacy signal emerged from a randomized, double-blind, placebo-controlled study; subsequent trials enrolled substantially larger populations; and a recent dose-response meta-analysis integrated the available randomized evidence using a formal statistical framework[1-4]. In addition, the clinical development program investigated several symptom domains rather than restricting assessment to positive symptoms alone. The inclusion of PANSS negative symptoms, BNSS, cognitive measures, and functional assessments is particularly relevant to the unmet therapeutic needs of schizophrenia.

Clinical and research significance

The significance of ulotaront extends beyond whether this individual compound ultimately demonstrates sufficient efficacy for clinical use. Its development tests the broader proposition that schizophrenia can be treated through modulation of neurotransmitter systems without direct D2-receptor blockade.

If future trials confirm clinically meaningful effects on psychosis, negative symptoms, cognition, or functioning with favorable tolerability, TAAR1-based pharmacology could represent an important expansion of therapeutic strategies. Conversely, continued failure to reproduce efficacy would indicate that mechanistic novelty alone is insufficient to overcome the biological complexity and heterogeneity of schizophrenia.

Conclusion

Ulotaront represents a promising non-D2-receptor-based pharmacological approach to the treatment of schizophrenia, primarily through TAAR1 agonism with additional 5-HT1A receptor activity. The available evidence demonstrates an initial therapeutic signal, with the pivotal phase II randomized trial showing a significant reduction in overall PANSS scores and exploratory improvements in positive and negative symptoms. However, these findings were not consistently reproduced in the subsequent phase III DIAMOND 1 and DIAMOND 2 trials, neither of which achieved its primary efficacy endpoint. The available dose-response meta-analytic evidence suggests a small potential benefit for overall psychopathology and negative symptoms**,** while the evidence for improvement in positive symptoms remains statistically uncertain. Evidence concerning cognitive impairment is currently insufficient to establish a definitive cognitive-enhancing effect, although exploratory studies have reported improvements in selected cognitive and functional measures. Ulotaront's absence of direct D2-receptor antagonism and the relatively limited extrapyramidal, prolactin, and metabolic effects observed in available studies provide an important rationale for continued

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investigation. Nevertheless, its clinical efficacy and long-term safety require confirmation through larger, adequately powered and independently controlled trials. Overall, current evidence supports ulotaront as an important investigational non-D2 therapeutic strategy**,** but does not yet establish a consistent efficacy profile across the major symptom domains of schizophrenia. Future research should focus particularly on persistent negative symptoms, cognition, functional recovery, dose optimization, active-comparator studies, and long-term controlled safety and efficacy.

Limitations

1. The number of randomized controlled trials evaluating ulotaront remains limited, reducing the precision and generalizability of pooled estimates.
2. The failure of the phase III DIAMOND trials to meet their primary endpoints introduced substantial heterogeneity and uncertainty in the efficacy findings.
3. Cognitive outcomes were inconsistently reported and were largely based on exploratory analyses, preventing a robust quantitative synthesis.
4. Long-term efficacy and safety evidence remains limited because much of the available extension data are open-label and lack a concurrent control group.

Declarations

Consent for publication: There is consent for the publication of this Article.

Authors' contributions: All authors contributed equally.

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